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46002	7590	07/26/2006	EXAMINER	
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10220 River Road, Suite 200			ART UNIT	
Potomac, MD 20854			PAPER NUMBER	
			1634	

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/823,784

Applicant(s)

UHLMANN ET AL.

Examiner

Amanda M. Shaw

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-34 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the amendment filed July 14, 2006. Applicant's arguments have been fully considered. All rejections not reiterated herein are hereby withdrawn. This action is non-final.

Claims 1-32 were previously presented. Claims 1, 11, and 24 have been amended. Claims 33 and 34 are new. Accordingly Claims 1-34 will be addressed herein.

THE FOLLOWING ARE NEW REJECTIONS.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 and 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding Claims 1-31 and 33-34 a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10

USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 1 and 12 recite the broad recitation "a sample comprising said nucleic acid molecule", and the claims also recite "a sample consisting of said nucleic acid molecule" which is the narrower statement of the range/limitation.

Claim 34 is rejected over the recitation of the phrase "wherein an allele frequency of 5% can be detected". This phrase is not considered to be an active process step and therefore fails to further limit the method of claim 10. This phrase appears to be a property of the method of claim 10.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-12, 19-28, 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al (Nucleic Acids Research 2000) in view of Nyren et al (U.S. Patent 6258568 Issued 2001).

Regarding Claim 1, Eads et al teach a method comprising treating a sample comprising genomic DNA with sodium bisulfite and amplifying the sample by fluorescent real time PCR to measure DNA methylation (Page I). The amplicon was then analyzed by bisulfite genomic sequencing in order to confirm methylation (Pages 3 and 7).

Eads et al do not teach a method wherein real-time sequencing is performed to determine the methylation status at a predetermined nucleotide position in the sample.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-43).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using pyrosequencing to confirm the methylation rather than genomic bisulfite sequencing in

order to achieve the benefits set forth by Nyren of using a sequencing method which enables a base to be identified at a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and the use of harmful radiolabels (Column 1). The method of Nyren can be used to determine base changes caused by methylation in samples treated with sodium bisulfite because the treatment converts unmethylated cytosine to uracil which gets amplified as thymine. Methylated cytosine remains unchanged and gets amplified as guanine. Therefore if an adenine gets incorporated then we would know that the cytosine was methylated. If a cytosine gets incorporated we would know that the cytosine was unmethylated.

Regarding Claim 2, Eads et al teach that twenty-five paired tumor and normal mucosal tissue samples were obtained from 25 patients with primary colorectal adenocarcinoma (Page 2).

Regarding Claims 3 and 4, Eads et al teach a method wherein the sample is derived from a tumor tissue, a neurodegenerative tissue or a tissue affected with another neurological disorder. Specifically the tissues used by Eads et al were from tumor tissues from colon and bladder cancer (Example 3).

Regarding Claim 5, Eads et al teach that the DNA is amplified by fluorescence-based real time PCR (Page 2).

Regarding Claims 6 and 7 Eads et al teach that the DNA is amplified by PCR.

However Eads et al does not teach that the one of amplification primers is detectably labeled with biotin, avidin, streptavidin or a derivative or a magnetic bead.

However, Nyren et al teach that DNA may be immobilization during amplification if one or more primers are attached to a support, or alternatively one or more of the PCR primers may carry a functional group permitting subsequent immobilization, eg. a biotin or thiol group (Column 8, lines 22-27).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using a primer labeled with a biotin in order to achieve the benefits set fourth by Nyren of providing a method which can be used to immobilize DNA for further analysis.

Regarding Claim 8, Eads et al teach a method used to analyze cytosine-5 methylation patterns (Abstract).

Regarding Claim 9, Eads et al teach a method comprising treating a sample comprising genomic DNA with sodium bisulfite and amplifying the sample by fluorescent real time PCR to measure DNA methylation (Page I). The amplicon was then analyzed by bisulfite genomic sequencing in order to confirm methylation (Pages 3 and 7).

Eads et al do not teach a method wherein real-time sequencing is performed to determine the methylation status at a predetermined nucleotide position in the sample.

However the real time pyrosequencing method of Nyren comprises: (a) hybridization of a sequencing primer to said amplified nucleic acid molecule in single-stranded form (Column 2, lines 25-29); (b) addition of a DNA polymerase, a ATP sulfurylase, a luciferase, an apyrase, adenosine-phosphosulfate (APS) and luciferin (Column 6, lines 60-65, Column 7, lines 1-5); (c) sequential addition of all four

Art Unit: 1634

different dNTPs (Column 2, lines 29-33) (d) detection of a luminescent signal wherein the intensity of the luminescent signal is correlated with the incorporation of a specific nucleotide at a specific position in the nucleic acid molecule (Column 2, lines 33-36).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using pyrosequencing to confirm the methylation rather than bisulfite genomic sequencing in order to achieve the benefits set forth by Nyren of using a sequencing method which enables a base to be identified at a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and the use of harmful radiolabels (Column 1).

Regarding Claim 10, Eads et al teach that fluorescent based real time PCT is used to quantify the methylated nucleotides (Page 2).

Regarding Claim 11, Eads et al teach that genomic DNA is treated with sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving any 5-methylcytosine residues unchanged (Page 1).

Regarding Claim 12 as noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of

Art Unit: 1634

the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present situation, the steps present in the method are able to stand alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a method for the diagnosis of a pathological condition or the predisposition for a pathological condition" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

Eads et al teach a method comprising treating a sample comprising genomic DNA with sodium bisulfite and amplifying the sample by fluorescent real time PCR to measure DNA methylation (Page I). The amplicon was then analyzed by bisulfite genomic sequencing in order to confirm methylation (Pages 3 and 7).

Eads et al do not teach a method wherein real-time sequencing is performed to determine the methylation status at a predetermined nucleotide position in the sample.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of a each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is

equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-43).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using pyrosequencing to confirm the methylation rather than genomic bisulfite sequencing in order to achieve the benefits set forth by Nyren of using a sequencing method which enables a base to be identified at a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and the use of harmful radiolabels (Column 1). The method of Nyren can be used to determine base changes caused by methylation in samples treated with sodium bisulfite because the treatment converts unmethylated cytosine to uracil which gets amplified as thymine. Methylated cytosine remains unchanged and gets amplified as guanine. Therefore if an adenine gets incorporated then we would know that the cytosine was methylated. If a cytosine gets incorporated we would know that the cytosine was unmethylated.

Regarding Claim 19, Eads et al teach that the nucleic acid molecule being detected is RNA or DNA (Page 2).

Regarding Claim 20, Eads et al teach that the DNA is amplified by fluorescence-based real time PCR (Page 2).

Regarding Claims 21 and 22 Eads et al teach that the DNA is amplified by PCR.

However Eads et al does not teach that the one of amplification primers is detectably labeled with biotin, avidin, streptavidin or a derivative or a magnetic bead.

However, Nyren et al teach that DNA may be immobilized during amplification if one or more primers are attached to a support, or alternatively one or more of the PCR primers may carry a functional group permitting subsequent immobilization, eg. a biotin or thiol group (Column 8, lines 22-27).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using a primer labeled with a biotin in order to achieve the benefits set forth by Nyren of providing a method which can be used to immobilize DNA for further analysis.

Regarding Claim 23, Eads et al teach that genomic DNA is treated with sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving any 5-methylcytosine residues unchanged (Page 1).

Regarding Claim 24, Eads et al teach a method comprising treating a sample comprising genomic DNA with sodium bisulfite and amplifying the sample by fluorescent real time PCR to measure DNA methylation (Page 1). The amplicon was then analyzed by bisulfite genomic sequencing in order to confirm methylation (Pages 3 and 7).

Eads et al do not teach a method wherein real-time sequencing is performed to determine the methylation status at a predetermined nucleotide position in the sample.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase

Art Unit: 1634

reaction in the presence of a each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-43).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using pyrosequencing to confirm the methylation rather than genomic bisulfite sequencing in order to achieve the benefits set fourth by Nyren of using a sequencing method which enables a base to be identified at a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and the use of harmful radiolabels (Column 1). The method of Nyren can be used to determine base changes caused by methylation in samples treated with sodium bisulfite because the treatment converts unmethylated cytosine to uracil which gets amplified as thymine. Methylated cytosine remains unchanged and gets amplified as guanine. Therefore if an adenine gets incorporated then we would know that they cytosine was methylated. If a cytosine gets incorporated we would know that the cytosine was unmethylated.

Regarding Claim 25, Eads et al teach that fluorescent based real time PCT is used to quantify the methylated nucleotides (Page 2).

Regarding Claim 26, Eads et al teach that genomic DNA is treated with sodium bisulfite to convert unmethylated cytosine residues to uracil residues while leaving any 5-methylcytosine residues unchanged (Page 1).

Regarding Claim 27, Eads et al teach a high through put assay to measure DNA methylation (Page 1).

Regarding Claim 28 Eads et al teach that twenty-five paired tumor and normal mucosal tissue samples were obtained from 25 patients with primary colorectal adenocarcinoma (Page 2).

Regarding Claim 30, Eads et al teach a method wherein said nucleotide is a cytosine and is part of one of a CpG island (Page 1).

Regarding Claims 31 and 33, Eads et al teach a high throughput assay which allows for rapid analysis of many samples at multiple gene loci (Page 2).

Regarding Claim 32 as noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the

present situation, the steps present in the method are able to stand alone and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of "a method for generating new nucleotide pairing partners upon amplification of at least one nucleic acid molecule for the detection of the methylation status of nucleotides of said nucleic acid molecule" merely sets forth the intended use or purpose of the claimed method, but does not limit the scope of the claims.

Eads et al teach a method comprising treating a sample comprising genomic DNA with sodium bisulfite and amplifying the sample by fluorescent real time PCR to measure DNA methylation (Page I). The amplicon was then analyzed by bisulfite genomic sequencing in order to confirm methylation (Pages 3 and 7).

Eads et al do not teach a method wherein real-time sequencing is performed to determine the methylation status at a predetermined nucleotide position in the sample.

However, Nyren et al teach a real time sequencing method called pyrosequencing that can be used to identify a base at a predetermined position in a DNA sample using an extension primer, which hybridizes immediately adjacent to the target position. The DNA sample and extension primer are subjected to a polymerase reaction in the presence of a each dNTP separately and the dNTPs will only become incorporated and release pyrophosphate (PPi) if it is complementary to the base in the target position. When the PPi is released a certain amount of light gets released that is equivalent to the amount of incorporated nucleotides. The unincorporated dNTPs get degraded (Column 2, lines 25-43).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using pyrosequencing to confirm the methylation rather than genomic bisulfite sequencing in order to achieve the benefits set forth by Nyren of using a sequencing method which enables a base to be identified at a target position and DNA to be sequenced simply and rapidly while avoiding the need for electrophoresis and the use of harmful radiolabels (Column 1). The method of Nyren can be used to determine base changes caused by methylation in samples treated with sodium bisulfite because the treatment converts unmethylated cytosine to uracil which gets amplified as thymine. Methylated cytosine remains unchanged and gets amplified as guanine. Therefore if an adenine gets incorporated then we would know that the cytosine was methylated. If a cytosine gets incorporated we would know that the cytosine was unmethylated.

Regarding Claim 34 it is an inherent property of the method that it can detect an allele frequency of 5%.

4. Claims 13-16, 18, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al (Nucleic Acids Research 2000), Nyren et al (U.S. Patent 6258568 Issued 2001) and in further view of Herman (U.S. Patent 5786146 Issued 1998).

The teachings of Eads et al and Nyren et al are presented above in paragraph 3.

Regarding Claims 13-16 and 18 the combined references do not teach that the methylation status is used to diagnose a pathological condition such as cancer, a neurodegenerative disease or another neurological disorder. The combined references also do not teach that they methylation status is used diagnose cancer that is a primary tumor, a metastasis or a residual tumor. The combined references do not teach that the primary tumor is a glioma selected from the group comprising: astrocytoma, oligodendroglioma, an oligoastrocytoma, a glioblastoma, a pilocytic astrocytoma. The combined references also do not teach that the neurological disorder is selected from the group comprising: Prader-Willi-Syndrome, Angelman-Syndrome, Fragile-X-Syndrome, or ATR-X-Syndrome.

However, Herman et al teaches that the detection of methylated CpG containing nucleic acid is indicative of several disorders. Such disorders include but are not limited to low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, colon cancer, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma. Identification of methylated CpG status is also useful for detection and diagnosis of genomic imprinting, fragile X syndrome and X-chromosome inactivation (Column 10).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method of Eads et al to diagnose pathological disorders. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of several pathological disorders. Accordingly, one of ordinary skill in the art would have been motivated to

Art Unit: 1634

have used the method of Eads in order to have achieved the advantage of being able to diagnose these diseases.

Regarding Claim 29 the combined references do not teach that the sample may be derived from blood serum or urine.

However, Herman et al teaches that if a sample is impure (i.e. such as plasma, serum, or blood) it may be treated before amplification with a reagent to open the cells, fluids, tissues or cell membranes to expose the DNA.

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Eads et al by using the method of Herman in order to achieve the benefit of being able to use a wider variety of sample types.

5. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Eads et al (U.S. Patent 6251594), Nyren et al (U.S. Patent 6258568) and in further view of Feinberg (Pub No. US 2003/0232351).

The teachings of Eads et al and Nyren et al are presented above in paragraph 3.

The combined references do not teach a method used to diagnose neurodegenerative diseases such as Alzheimer's disease, Parkinson disease, Huntington disease, or Rett-Syndrome.

However, Feinberg teaches a method of determining a disease state in a subject by determining DNA methylation status. Although the disease state is often cancer, the

methods taught by Feinberg also include Alzheimer's disease and Parkinsons disease (Paragraph 0029).

Accordingly it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the method that Eads et al used to diagnose primary tumors, to also diagnose neurodegenerative diseases. It was well known in the art at the time the invention was made that the detection of methylated sequences is indicative of certain neurodegenerative diseases. Accordingly, one of ordinary skill in the art would have been motivated to use the method of Eads in order to have achieved the advantage of being able to diagnose these diseases.

Conclusion

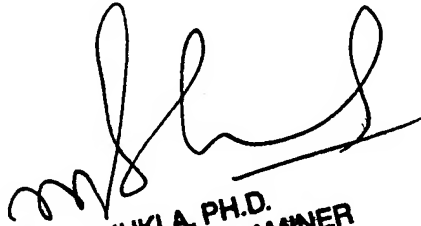
6. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1634

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634



RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER